IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Gans, et al

Serial No. 10/037,360

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Art Unit: 1617

Examiner: Mojdeh Bahar

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COMPOSITIONS AND METHODS FOR ENHANCING CORTICOSTERIOD DELIVERY

Commissioner for Patents
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Sir:

DECLARATION

1. I, Dr. Eugene H. Gans, am a named inventor of the above-referenced patent application. I received a Bachelor of Science (B.S.) in 1951 from Columbia University New York, New York; a Master of Science (M.S.) in 1953 from Columbia University New York, New York; a Doctor of Philosophy (Ph.D.) in 1956 from the University of Wisconsin Madison, Wisconsin. Starting in 1956 and continuing to the present, I have been involved in the development and testing of dermatologic drug delivery systems. I am presently a Senior Advisor to Medicis Pharmaceutical Corp. and am involved in the development and licensing of cosmetic and drug delivery systems. For several years, beginning in 1989, I had been a member of the AAPS/FDA/NIH/Academia/Industry Planning Committee to Establish Criteria for Assessing the Absorption of Active Agents & Drugs Into and Within the Skin.

2. When applied to the skin, topical corticosteroids produce a localized skin-blanching response, caused by constriction of the superficial blood vessel of the skin. (*See* Stoughton RB. Vasoconstrictor assay-specific applications. In: Maibach HI, Surber C. eds.

Topical Corticosteroids. Basel:Karger; 1992:42-53; McKenzie AW, Stoughton RB. Method for Comparing Percutaneous Absorption of Steroids. *Arch Dermatol.* 1962; 86:608-610.) (attached as Exhibit A). The degree of skin blanching, which can be assessed by careful visual scoring, serves as a measure of the inherent potency of the drug and its capacity to diffuse through the stratum corneum, and is known by one skilled in this field.

3. The vasoconstrictor assay is the most widely used technique to assess the potency of topical corticosteroid compositions. It correlates well with the clinical efficacy of corticosteriod formulations. Workers in this field use it to identify and optimize new formulations for clinical development.

4. The U.S. FDA requires the submission of *in vivo* bioequivalence in abbreviated new drug applications (ANDA) for topical corticosteriod compositions. (21 C.F.R. § 320) of various potency groups. Guidance from the FDA, effective June 2, 1995, recommends that vasoconstrictor assays be used for this purpose. The FDA publication further states that "[m]ost of the currently available generic topical corticosteroids have been approved on the basis of [a vasoconstrictor bioassay]." (See Guidance for Industry, Center for Drug Evaluation and Research, Food and Drug Administration, page 3 (1997), *available at* <http://www.fda.gov/cder/guidance/old098fn.pdf>) (attached as Exhibit B).

5. The relative potency of topically applied corticosteroids are ranked by class, based on vasoconstrictor testing, with Class I being the most potent and Class VI being the least potent. (See Anti-inflammatory Agents, American Hospital Pharmacy Service (AHFS) Drug Information Manual, page 3403 (2003) (the "AHFS Manual")) (attached as Exhibit C).

6. As is known to persons skilled in this field, activity of a topical corticosteriod preparation may vary greatly and unpredictably based, in part, on the vehicle or

formulation. The AHFS Manual further points out that "*activity may vary considerably depending upon the vehicle.*" Id. (Italics in original). As shown in the AHFS Manual, the topical coricosteroid betamethasone dipropionate exists in each of Class III, II and I, even though the listed concentration of betamethasone dipropionate in each preparation in the same 0.05%. Id.

7. The anti-inflammatory activity of topical corticosteroid compositions is based upon differences in vasoconstrictor test scores. (AHFS Manual, page 3403). For example, Class I topical corticosteroid compositions often exhibit a vasoconstrictor score of 80 or above, while Class II topical corticosteroid compositions often exhibit a vasoconstrictor score of less than 80. Further, the more potent Class 1 topical corticosteroid compositions are restricted in their use because of the clinical potential to induce adrenal cortex suppression. Thus, the clinical and physiological differences between, for example, Class I and Class II topical corticosteroid compositions, is also manifested by the different restrictions that FDA places on their use.

8. The FDA requires the submission of vasoconstrictor scores in NDA, (See Guidance for Industry, *supra*) and, very importantly, one must show that the vasoconstrictor score is comparable in magnitude to the vasoconstrictor test score produced by an already FDA approved, topical vasoconstrictor in the desired class. For example, in a new drug application requesting approval of a product according to the present invention as a Class I - topical corticosteroid composition, it must produce a vasoconstrictor score comparable to an already FDA approved vasoconstrictor, for instance, Clobetasol®. In these tests, the score for Clobetasol® was above 80, and thus, scores below 80 are not acceptable to FDA as demonstrating Class I activity, as epitomized by Clobetasol®. More specifically, the commercially available topical fluocinonide composition Lidex®, which has a vasoconstrictor score of less than 80, is currently classified as a Class II steroid.

9. Thus, the difference in vasoconstrictor scores of 71 and 85 for fluocinonide represents real, clinical and physiological differences by placing topical fluocinonide in specified vehicles producing these scores into separate classes. As illustrated in the present invention, the average of summed vasoconstrictor score of 85 was the result of a ratio of penetration enhancers, to (penetration enhancers and solvents and emulsifiers) of at least about 0.90 versus an average of summed vasoconstrictor scores of 71 for of a ratio of penetration enhancers, to (penetration enhancers and solvents and emulsifiers) of at least about 0.80 (see Table 2, paragraph 26 of the present application). The effect of altering of the ratio of penetration enhancers, to (penetration enhancers and solvents and emulsifiers) which provides for the rise in vasoconstrictor scores from 71 to 85, with the associated rise from Class II to Class I, is an entirely unexpected result.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully Submitted,

Dated: 2/23/04

Dr. Eugene H. Gans